Virginia Department of Health
Q Fever: Guidance for Healthcare Providers
Key Medical and Public Health Interventions after Identification of a Suspected Case

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1. Epidemiology

Q fever is a zoonotic bacterial disease caused by *Coxiella burnetii*, an obligate intracellular gram-negative bacterium. The organism can form a spore-like stage that is highly resistant to heat, drying and many commonly-used disinfectants and can persist in the environment for years. *C. burnetii* is highly infectious when aerosolized and inhaled; a single organism might cause clinical illness. *C. burnetii* is designated as a Category B bioterrorism agent (i.e.,are considered to be moderately easy to disseminate or transmit and are associated with moderate morbidity and a lower rate of mortality than Category A agents). *C. burnetii* is also designated as a select agent or toxin which means that it could be developed for bioterrorism and that possession, use or transfer of these organisms requires registration with the Centers for Disease Control and Prevention (CDC) or the U.S. Department of Agriculture (USDA).

Cattle, sheep and goats are the natural reservoir for *C. burnetii*; however, a variety of other animals (e.g., wildlife, marine mammals, domestic mammals, birds, reptiles) can be infected. Most infected animals are asymptomatic. The highest number of organisms is shed by infected animals during birthing in amniotic fluids and the placenta; organisms are also 4excreted in milk, urine and feces of infected animals. *C. burnetii* has been isolated from approximately 40 tick species. Possible tickborne transmission to humans has been reported, but it is not thought to be a common mode of transmission to humans.

Q fever infections occur worldwide. In the United States, 156 cases (122 acute cases and 34 chronic cases) were reported to CDC in 2015. Infections occur year-round, but they typically peak in the spring, which coincides with the birthing season for livestock. The incidence of disease in the United States increases with age and males tend to develop disease more often than females. In Virginia, an average of 2.0 cases per year was reported during 2011–2015 and no cases were reported in 2016.

Q fever is primarily an occupational hazard related to working with animals (e.g., livestock farms, meat processing plants, slaughterhouses, veterinary clinics, research facilities with pregnant sheep) or living in a rural area or near farms with livestock. Infection most commonly occurs through inhalation of the organism in fine-particle aerosols generated from birth products or fluids during birthing. Infection can also occur through inhalation of dust contaminated with infective birth products, milk or excreta (e.g., urine and feces). Less common routes include contact with the birth products, tissue, wool, or bedding from infected animals; laboratory exposure through parenteral inoculation or exposure to infectious aerosols or droplets; ingestion of unpasteurized dairy products from infected animals; transfusion of contaminated blood or bone marrow; and possibly tick bites. Airborne particles can travel for miles, generating sporadic cases or outbreaks without apparent animal contact. Person-to-person transmission of *C. burnetii* is rare, but has been reported with sexual contact, placental transmission, blood transfusion or tissue transplantation and healthcare-associated transmission during autopsies and obstetrical procedures.

2. Clinical Manifestations

Q fever can cause acute or chronic illness in humans and each of these forms is described below.

Acute Q Fever

- Incubation period: Dose-dependent, but typically 2–3 weeks (range: 3 days –6 weeks) after exposure
- Signs and Symptoms: Variable presentation. Up to half of infected persons are asymptomatic.
- A common presentation of acute Q fever is a self-limited febrile influenza-like illness lasting 2–14 days. The fever usually peaks within 2–4 days, and then resolves after 5–14 days. However, fever can last more than 57 days; therefore, acute Q fever is also a cause of prolonged fever of unknown etiology. In addition to fever, signs and symptoms can include abrupt onset of fatigue, cough, malaise, chills, sweats, myalgia and headache. Nausea, vomiting, chest pain, diarrhea, sore throat and rash have been less frequently reported.
- Another presentation of acute Q fever is pneumonia. This may appear as atypical pneumonia, rapidly progressive pneumonia (mimicking Legionnaire's disease), or most commonly, pneumonia with fever but no pulmonary symptoms. When present, pulmonary symptoms can include a nonproductive cough, hemoptysis or pleuritic chest pain. Signs are often minimal, and might include inspiratory crackles or splenomegaly.
- Less common presentations of acute Q fever can include hepatitis (fever, abdominal pain, anorexia, nausea, vomiting, diarrhea and jaundice), myocarditis, pericarditis, meningitis, encephalitis or nonspecific skin rash. Q fever in pregnant women mainly causes placentitis; cases may be asymptomatic, but generally present with fever. Q fever in pregnancy can cause spontaneous abortion or premature labor.
- The estimated case fatality rate of acute Q fever is low (< 2%). Treatment with an appropriate antibiotic can shorten the course of illness for acute Q fever.

Chronic Q fever

- Incubation period: Months to years after initial exposure. Chronic Q fever can present within weeks after an acute infection or manifest many years later.
- Signs and Symptoms: Variable presentation
- Chronic Q fever is a severe disease occurring in <5% of acutely infected patients. Although anyone with acute Q fever is at risk of developing chronic Q fever, the groups at highest risk for chronic Q fever are pregnant women, immunosuppressed persons and patients with pre-existing heart valve defects, arterial aneurisms, or vascular grafts.

- Endocarditis, the major clinical presentation of chronic Q fever, comprises 60%–70% of all reported chronic cases.
- Nonspecific presentations of chronic Q fever may include a generalized illness characterized by a low-grade fever, often remittent and well tolerated, which may be associated with malaise, weakness, fatigue, weight loss, chills, anorexia or night sweats. Manifestations may include digital clubbing, purpuric rash (extremities and mucosa), splenomegaly, hepatomegaly, chronic renal insufficiency, microscopic hematuria and/or embolic manifestations (stroke). Cases may also present with symptoms of heart failure or cardiac valve dysfunction (dyspnea, acute pulmonary edema, angina, palpitations, and heart murmur).
- Other manifestations of chronic Q fever include chronic hepatitis, vasculitis, osteomyelitis, osteoarthritis, chronic pulmonary infection (fibrosis) or post-Q fever fatigue syndrome, which has been reported to occur in 10%–25% of some acute patients and is characterized by constant or recurring fatigue, night sweats, severe headaches, photophobia, pain in muscles and joints, mood changes, and difficulty sleeping.

3. Laboratory Testing and Diagnosis

Notification when Q Fever is Suspected

If Q fever is suspected, the healthcare provider should immediately report the case to the local health department per Virginia's disease reporting regulations. The local health department will discuss options for public health testing. If VDH approves public health testing, specimens may be sent to the Division of Consolidated Laboratory Services (DCLS). The health department will facilitate notification and shipment to DCLS. Specimens potentially containing *C. burnetti* should **never** be shipped to DCLS without prior approval.

Laboratory Biosafety

If Q fever is suspected, laboratory personnel **must** be alerted to ensure safe specimen processing and selection of appropriate diagnostic tests. Routine bacteriologic testing will not detect *C. burnetii*. *C. burnetii* is highly infectious and presents a significant risk of laboratory infection because of the potential for inhalation of organisms. Biosafety Level 2 practices and facilities are appropriate for nonpropagative laboratory procedures, including serologic testing and staining of impression slides. However, Biosafety Level 3 practices are necessary for activities involving culture, necropsy of infected animals, generation of aerosols or any manipulation of infected tissues. BSL-3 precautions include wearing personal protective equipment (PPE) (e.g., gown, gloves, and face/eye protection) and respiratory protection. Because *C. burnetii* can grow in a variety of cell lines, it may inadvertently be cultured if infected specimens are placed into routine viral culture.

Sample Collection

Sample collection instructions for testing at DCLS (and potentially at CDC) are shown in Table 1. Because of the highly infectious nature of this organism, consultation with DCLS about specimen collection and handling is strongly recommended. The DCLS Emergency Officer can be reached 24 hours a day/7 days a week at 804-335-4617.

Table 1. Sample Collection Instructions for Testing Suspected Q Fever*

Test and Turnaround Time	Acceptable samples	Amount	Instructions
Coxiella burnetii serology (Indirect fluorescence assay. performed at CDC) Estimated turnaround time: 6 weeks upon specimen receipt	Serum (acute and convalescent)	2-3 mL	Collect acute serum (during active stage of illness as close to onset as possible) and convalescent serum (2–4 weeks after acute stage). Collect in red top or tiger top tube. Remove serum and place in sterile tube. Acute and convalescent specimens can be shipped together (refrigerate acute specimen until convalescent specimen has been collected and is ready for shipment; ship both specimens refrigerated on cold packs); if specimen(s) was previously frozen, then ship frozen on dry ice.
Coxiella burnetii molecular detection (PCR, performed at DCLS) Estimated turnaround time: 1 business day upon specimen receipt	Blood (acute sample) Collect before antimicrobial therapy, if possible	10 cc	Collect blood in purple top (EDTA) blood collection tube. Ship refrigerated on cold packs. Note that negative test result does not rule out infection.
	Serum (acute sample)	2-3 mL	Collect in red top or tiger top tube. Remove serum and place in sterile tube. Ship refrigerated on cold packs. Note that negative test result does not rule out infection.
	Fresh tissue (e.g., heart valve) biopsy	1 gram	Place tissue on sterile gauze pads moistened with sterile saline in a collection cup. Ship refrigerated on cold packs. Note that negative test result does not rule out infection.
Immunohistochemistry Assay (performed at CDC) Estimated turnaround time: 8 weeks upon specimen receipt	Fresh tissue (e.g., heart valve)	--	Biopsy tissue should be delivered as fresh tissue to laboratory; CDC accepts formalin-fixed, paraffin-embedded tissues for testing

* Adapted from American Society for Microbiology's Sentinel level clinical laboratory guidelines for suspected agents of bioterrorism and emerging infectious diseases: Coxiella burnetii (2016). If Q fever is suspected, notify the local health department immediately to discuss the case and laboratory testing. If VDH approves public health testing, specimens may be sent to Division of Consolidated Laboratory Services (DCLS) with the DCLS Clinical Microbiology/ Virology Request Form; include the name of the test on the form (e.g., Q fever serology). For questions about collecting specimens or for notifying DCLS when submitting specimens, contact the DCLS Emergency Officer available 24/7 at 804-335-4617. Of note, culture of blood or fresh tissue requires a biosafety level 3 (BSL-3) laboratory and is not recommended for routine diagnosis.

Diagnosis

Diagnosis of Q fever requires specific testing because clinical manifestations are highly variable and nonspecific. Diagnosis of acute and chronic Q fever is based mainly upon serologic testing to detect a 4-fold or greater change in antibodies to *C. burnetii* phase I and phase II antigens, in combination with *C. burnetii* DNA detection by PCR. The reference method for serologic diagnosis is indirect immunofluorescence assay (IFA). For a definitive diagnosis during the early stages of acute illness,

serologic testing of acute and convalescent serum samples is needed to detect a 4-fold or greater change in phase II IgG titer. In the acute phase of illness, the antibody level to phase II IgG antigen is elevated and is usually higher than that to phase I IgG antigen; in chronic Q fever, the phase I IgG titer is elevated and is typically higher than phase II IgG titer.

Ideally the acute specimen should be collected during the first week of illness; however, results are often negative or too low for detection, but do not rule-out infection and are not helpful for guiding immediate treatment decisions. Therefore, storing the acute phase serum until a convalescent specimen has been collected (2–4 weeks after the acute stage) is recommended so that simultaneous testing at the same laboratory can be performed. Immunoglobulin M (IgM) antibodies to phase II antigen develop in the second week of acute illness, with an increase in phase II IgG occurring almost simultaneously. In successfully treated or spontaneously resolving disease, IgG and IgM titers to phase I antigen might continue to increase in later specimens but typically do not exceed phase II titers. Antibodies might remain detectable for many months, for years, or for life.

PCR of whole blood or serum can be positive early after symptom onset (acute phase of illness) and is most sensitive during the first week of symptom onset, but sensitivity rapidly decreases as the antibody titer increases and after administration of antibiotics. Infected tissue (e.g., heart valve in Q fever endocarditis) may be tested by PCR, immunohistochemistry, or culture (with appropriate consultation). Of note, a negative PCR result does not rule-out a Q fever diagnosis and treatment should not be withheld based on a negative result. Culture is not recommended for routine diagnosis because the process is difficult, time-consuming, and requires a BSL-3 laboratory. In certain circumstances, culture can be performed at CDC after consultation with the local health department and DCLS. Immunohistochemistry assays at CDC are available to detect *C. burnetii* antigens in formalin-fixed, paraffin-embedded tissues (e.g., heart valve specimens).

Case Definitions used by Public Health

The current CDC case definition for acute and chronic Q fever is available at http://wwwn.cdc.gov/nndss/script/casedefDefault.aspx. Note that a case definition is set of uniform criteria used to define a disease for public health surveillance. Case definitions enable public health to classify and count cases consistently across reporting jurisdictions and they should not be used by healthcare providers to determine how to meet an individual patient's health needs.

4. Treatment

Treatment recommendations for acute and chronic Q fever are summarized in Table 2. Doxycycline is the treatment of choice for non-pregnant adults with Q fever. When tetracyclines are contraindicated (i.e., pregnant women, children aged <8 years), other antibiotics may be used, such as trimethoprim/sulfamethoxazole, fluorquinolones or macrolides. Treatment is most effective if given within the first 3 days of illness. Because of the delay in seroconversion often necessary to confirm diagnosis, antibiotic treatment of acute Q fever not be withheld pending laboratory tests or discontinued on the basis of a negative acute specimen. In addition to treatment, serologic monitoring is recommended following acute Q fever infection to assess possible progression to chronic infection. The recommended schedule for monitoring is based on the patient's risk for chronic infection (i.e., considering vascular and heart valve defects, immunosuppressive conditions, and pregnancy status). For more information, refer to CDC's Diagnosis and Management of Q Fever — United States, 2013.

CDC recommends that treatment of chronic Q fever should be initiated only after diagnostic confirmation. For chronic Q fever infections, management by an infectious disease specialist is recommended because of long-term antibiotic therapy, serologic monitoring and periodic diagnostic testing.

Treatment of asymptomatic or resolved infections is not routinely recommended by CDC, but it might be considered in patients with risk factors for developing chronic Q fever infections (refer to CDC's Diagnosis and Management of Q Fever — United States, 2013 for more information).

Table 2. Recommended treatment regimens for acute and chronic Q fever*

Indication	Adults	Children[¶]	Pregnant women
Acute Q Fever	Doxycycline[§] 100 mg twice a day for 14 days	≥8 years: Doxycycline: 2.2 mg/kg per dose twice a day for 14 days (maximum 100 mg per dose) <8 years with high risk criteria[**]: Doxycycline: 2.2 mg/kg per dose twice a day for 14 days (maximum: 100 mg per dose) <8 years with mild or uncomplicated illness: Doxycycline 2.2 mg/kg per dose twice a day for 5 days (maximum 100 mg per dose). If patient remains febrile past 5 days of treatment: trimethoprim/sulfamethoxazole 4–20 mg/kg/ 24 hours (dose based on trimethoprim component) in equally divided doses every 12 hours (maximum: 320 mg trimethoprim per 24 hours)	Trimethoprim/sulfamethoxazole:160 mg/800 mg twice a day throughout pregnancy but not beyond 32 weeks' gestation[††]
Chronic Q fever			
Endocarditis or vascular infection	Doxycycline[§§] 100 mg twice a day and hydroxychloroquine[¶¶] 200 mg three times a day ≥18 months	Recommend consultation[***]	Recommend consultation[†††]
Noncardiac organ disease[§§§]	Doxycycline 100 mg twice a day and hydroxychloroquine 200 mg three times a day	Recommend consultation[***]	Recommend consultation[†††]
Postpartum[¶¶¶] with serologic profile for chronic Q fever	Doxycycline 100 mg twice a day and hydroxychloroquine 200 mg three times a day for 12 months	--	--
Post-Q fever fatigue syndrome[****]	No current recommendations	No current recommendations	No current recommendations

Source: CDC. Diagnosis and Management of Q Fever — United States, 2013. MMWR 2013; 62(No. RR-03):[1–29]. Available at http://www.cdc.gov/mmwr/pdf/rr/rr6203.pdf and Errata: Diagnosis and Management of Q Fever — United States, 2013. MMWR 2013; 62(35); 730. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6235a8.htm?s_cid=mm6235a8_w.
For additional information on dosing, please consult with the package inserts.

*All drug dosages are oral regimens. Prophylactic treatment after a potential Q fever exposure is not recommended; treatment is not recommended for asymptomatic infections or after symptoms have resolved, although it might be considered in persons at high risk for development of chronic Q fever.

[§] Patients may take doxycycline with food to avoid stomach upset but should have no dairy products within 2 hours (before or after) of taking medication. Doxycycline should not be taken with antacids or bismuth-containing products, and patients should avoid taking it immediately before going to bed or lying down. Doxycycline might cause photosensitivity and can decrease the efficacy of hormonal contraceptives.

[¶] Doxycycline is the drug of choice for treatment of Q fever in adults and patients of any age with severe illness. Short courses (≤5 days) for treatment of rickettsial infections have not been shown to result in significant dental staining in children; however, whether a 2-week course will cause permanent tooth discoloration in children is unknown. Health-care providers should use their clinical judgment to determine appropriate therapy in children aged <8 years and may consider treatment with trimethoprim/sulfamethoxazole or a shorter duration of doxycycline (5 days) in children with a mild or uncomplicated illness. Trimethoprim/sulfamethoxazole is contraindicated in children aged <2 months.

[**] Children aged <8 years who are considered high risk and should therefore receive the full 14-day treatment with doxycycline include children who are hospitalized or have severe illness, children with preexisting heart valvulopathy, children who are immunocompromised, or children with delayed Q fever diagnosis who have experienced illness for >14 days without resolution of symptoms.

[††]Limited data are available on treatment of Q fever during pregnancy. Consultation with an expert in infectious diseases is recommended. Trimethoprim/sulfamethoxazole should be discontinued for the final 8 weeks of pregnancy because of the risk for hyperbilirubinemia.

[§§] Target serum levels for optimal efficacy during chronic Q fever treatment is ≥5 µg/mL.

¶¶Take with food or milk. Should not be used by persons with glucose-6-phosphate dehydrogenase deficiency. Monitor for retinal toxicity. Target serum levels for optimal efficacy is 1.0+0.2 µg/mL. The safety of long-term treatment in children has not been evaluated.

***Limited data are available on treatment of chronic Q fever in children. Consultation with an expert in pediatric infectious diseases is recommended.

†††The safety of long-term doxycycline or hydroxychloroquine treatment in pregnant women and fetal risk has not been evaluated. Consultation with an expert in infectious diseases and obstetrics is recommended.

§§§ Limited reports of treatment for chronic Q fever unrelated to endocarditis or vascular infection (e.g., osteoarticular infections or chronic hepatitis); duration of treatment is dependent on serologic response. Consultation with expert in infectious diseases is recommended.

¶¶¶Women should only be treated postpartum if serologic titers remain elevated >12 months after delivery (immunoglobulin G phase I titer ≥1:1024). Women treated during pregnancy for acute Q fever should be monitored similarly to other patients who are at high risk for progression to chronic disease (e.g., serologic monitoring at 3, 6, 12, 18, and 24 months after delivery).

****Reports of treatment studies are rare. Although limited success has occurred with long-term or pulsed tetracycline-class antibiotics, evidence to guide patient management is weak.

5. Postexposure Prophylaxis

Postexposure prophylaxis (PEP) following an exposure to naturally occurring *C. burnetii* and before symptom onset is not recommended by CDC. A daily fever monitoring log should be kept for a minimum of 3 weeks after exposure and routine serologic screening to monitor high-risk persons (e.g., immunosuppression, pregnancy, and valvulopathies) might be recommended. If a fever occurs within 6 weeks of exposure, immediate medical evaluation and treatment with doxycycline (ideally within 24 hours of fever onset) and testing are recommended. See CDC's. Diagnosis and Management of Q Fever — United States, 2013 for additional information).

If an intentional release of *C. burnetii* was suspected, PEP (doxycycline 100 mg twice a day for 5-7 days) can be considered in those determined to be at high risk for exposure. PEP would be considered effective only if administered within 8-12 days of the exposure.

6. Vaccination

In the United States, a Q fever vaccine is not commercially available.

7. Infection Control

For infection control, Standard Precautions are adequate for routine care of patients with Q fever. Additional precautions should be used depending on the situation. If splashes of infected material are anticipated (e.g., during delivery of an infant from an infected woman), then a face mask and eye protection (goggles or face shield) are recommended. If aerosol-generating procedures are performed, then additional precautions are needed. These include wearing a fit-tested N-95 respirator (or equivalent) and goggles or a face shield for eye protection and performing the procedure in an airborne infection isolation room, if available. If an autopsy is being conducted on a person who died of Q fever, then a BSL-3 facility should be used or barrier precautions of BSL-2 and the negative airflow and respiratory precautions of BSL-3 should be used. See CDC. Diagnosis and Management of Q Fever — United States, 2013 for additional information).

8. Decontamination

C. burnetii may survive for months or years in its spore form, and can resist heat, desiccation and many commonly used disinfectants (e.g., bleach). Therefore, special decontamination procedures are necessary for surfaces potentially contaminated with *C. burnetii*. Minor spills should be covered with absorbent paper, such as paper towels, and then flooded with 70% - 95% ethanol or 5% MicroChem-Plus (a dual quaternary ammonium/detergent compound which should be allowed to act for 30 minutes before cleanup). Spills that involve high concentrations of organisms, include organic matter, or occur in areas of lower temperatures (e.g., refrigerators or freezers), should be exposed to disinfectant solution for 1 hour before cleanup. Proper personal protective equipment (PPE) should be worn during cleaning and disinfection.

Hospital rooms of patients with Q fever should receive terminal cleaning consistent with the above precautions, and clothing or linens should be handled to minimize aerosolization and disinfected according to hospital protocol.

9. Postmortem Practices

If Q fever is suspected as a cause of death, the district Office of the Chief Medical Examiner should be immediately notified. Consultation should occur regarding whether an autopsy should be conducted, parties responsible for conducting the autopsy, and proper personal protective procedures to follow.

10. Public Health Measures

- Suspected or confirmed Q fever cases should be reported immediately to the local health department.
- Laboratory specimens should be sent to the state public health laboratory (DCLS) for confirmation of agent and other studies after VDH consultation and approval.
- Designated public health authority should begin an epidemiologic investigation.
  - Collect detailed information from the patient to attempt to identify the source of the exposure.
  - Investigate contacts of the case-patient for compatible illness to investigate a potential common exposure.
  - Suspected food items (e.g., milk) might be collected for testing. VDH's Office of Epidemiology will work with the Food and Drug Administration if commercially prepared food is implicated.
  - If animal exposures are identified, Virginia Department of Agriculture and Consumer Services will be notified.
  - Implement control measures to prevent disease and additional exposures. For laboratorians or others potentially exposed who might have worked with the agent before identification as *C. burnetii,* PEP and postexposure monitoring might be recommended based on a risk assessment.
  - VDH will work with the CDC, Federal Bureau of Investigation (FBI) and other state or federal agencies as necessary.

11. References and Resources

American Society for Microbiology (ASM). Sentinel level clinical laboratory guidelines for suspected agents of bioterrorism and emerging infectious diseases: *Coxiella burnetii*. Revised March 2016. Available at https://www.asm.org/Articles/Policy/Laboratory-Response-Network-(LRN)-Sentinel-Level-C (accessed February 15, 2019).

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